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ORIGINAL ARTICLE

Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: Data from the international SWEET registry

Claudio Maffeis[1] | Niels H. Birkebaek[2] | Maia Konstantinova[3] | Anke Schwandt[4,5] | Andriani Vazeou[6] | Kristina Casteels[7,8] | Sujata Jali[9] | Catarina Limbert[10] | Auste Pundziute-Lycka[11] | Peter Toth-Heyn[12] | Carine de Beaufort[13] | Zdenek Sumnik[14] | Valentino Cherubini[15] | Jannet Svensson[16] | Daniele Pacaud[17] | Christina Kanaka-Gantenbein[18] | Shlomit Shalitin[19,20] | Natasa Bratina[21] | Ragnar Hanas[22] | Guy T. Alonso[23] | Luxmi Poran[24] | Ana L. Pereira[25] | Marco Marigliano[1] | The SWEET Study Group

[1]Pediatric Diabetes and Metabolic Disorders Unit, University of Verona, University City Hospital, Verona, Italy

[2]Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark

[3]Clinic for Endocrinology, Diabetes and Genetics, Medical University Sofia, University Pediatric Hospital, Sofia, Bulgaria

[4]Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany

[5]German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany

[6]Diabetes Center, P & A Kyriakou Children's Hospital, Athens, Greece

[7]Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

[8]Department of Development and Regeneration, University of Leuven, Leuven, Belgium

[9]KLE Diabetes Centre, KLE University JNMC and KLE'S Dr. Prabhakar Kore Hospital & MRC, Belagavi, India

[10]Hospital Dona Estefânia, Unit of Pediatric Endocrinology and Diabetes, Lisbon, Portugal

[11]Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden

[12]Ist. Department of Pediatrics, Semmelweis University, Budapest, Hungary

[13]Deccp, Pediatric Clinic/Centre Hospitalier de Luxembourg, Luxembourg, Grand Duche de Luxembourg

[14]Department of Pediatrics, Motol University Hospital, Prague, Czech Republic

[15]Department of Women's and Children Health, Salesi Hospital, Ancona, Italy

[16]Department of Pediatric and adolescents, Copenhagen University hospital, Herlev, Denmark

[17]Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta, Canada

[18]Diabetes Center, First Department of Pediatrics, Medical School,National and Kapodistrian University of Athens, Agia Sophia Children's Hospital, Athens, Greece

[19]The Jesse Z. and Lea Shafer Institute of Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel

[20]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[21]University Children's Hospital, Department of Endocrinology, Diabetes and Metabolic Diseases, Ljubljana, Slovenia

[22]The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and NU Hospital Group, Uddevalla, Sweden

[23]Barbara Davis Center, University of Colorado, Aurora, Colorado

[24]General Private Practitioner at T1diams, Mauritius, Island

[25]APDP-Diabetes Portugal, Department of Pediatric and adolescents, Lisbon, Portugal

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; BMI-SDS, body mass index SD score; CSII, continuous subcutaneous insulin infusion; CT, conventional therapy; DCCT, diabetes control and complications trial; EDIC, epidemiology of diabetes interventions and complications; FDR, false discovery rate; HbA1c, glycated hemoglobin; ICT, intensified conventional therapy; MOM, multiple of the mean; NW, normal weight; OB, obese; OW, overweight; T1D, type 1 diabetes; UW, underweight; WHO, World Health Organization

Correspondence
Prof. Claudio Maffeis, Pediatric Diabetes and Metabolic Disorders Unit, Regional Center for Pediatric Diabetes, University Hospital, Piazzale Stefani 1, 37126 Verona, Italy.
Email: claudio.maffeis@univr.it

Objective: To assess the prevalence of underweight (UW), overweight (OW), and obesity in children and adolescents with type 1 diabetes (T1D).

Methods: An international cross-sectional study including 23 026 T1D children (2-18 years, duration of diabetes ≥1 year) participating in the SWEET prospective, multicenter diabetes registry. Body mass index SD score (BMI-SDS) was calculated using the World Health Organization BMI charts. Children were categorized as UW (BMI-SDS < −2SD), OW (+1SD < BMI-SDS ≤ +2SD), and obese (OB) (BMI-SDS > +2SD). Hierarchic regression models were applied with adjustment for sex, age, and duration of diabetes.

Results: The prevalence of UW, OW, and obesity was: 1.4%, 22.3%, and 7.3% in males and 0.6%, 27.2%, and 6.8% in females. Adjusted BMI-SDS was significantly higher in females than in males (mean ± SEM: 0.54 ± 0.05 vs 0.40 ± 0.05, $P < 0.0001$). In males, BMI-SDS significantly decreased by age ($P < 0.0001$) in the first three age categories 0.61 ± 0.06 (2 to <10 years), 0.47 ± 0.06 (10 to <13 years), 0.34 ± 0.05 (13 to <16 years). In females, BMI-SDS showed a U-shaped distribution by age ($P < 0.0001$): 0.54 ± 0.04 (2 to <10 years), 0.39 ± 0.04 (10 to <13 years), 0.55 ± 0.04 (13 to <16 years). BMI-SDS increased by diabetes duration (<2 years: 0.38 ± 0.05, 2 to <5 years: 0.44 ± 0.05, and ≥5 years: 0.50 ± 0.05, $P < 0.0001$). Treatment modality did not affect BMI-SDS. Adjusted HbA1c was significantly higher in females than in males (8.20% ± 0.10% vs 8.06% ± 0.10%, $P < 0.0001$). In both genders, the association between HbA1c and BMI-SDS was U-shaped with the highest HbA1c in the UW and obesity groups.

Conclusions: The high rate of OW and obesity (31.8%) emphasize the need for developing further strategies to prevent and treat excess fat accumulation in T1D.

KEYWORDS

children, obesity, overweight, prevalence, type 1 diabetes

1 | INTRODUCTION

In the last decades, a rapid increase in the prevalence of obesity in children and adolescents has occurred worldwide.[1,2] Similarly, an increase in the prevalence of type 1 diabetes (T1D) was also observed.[3,4] The obesogenic environment is likely to play a role in this process.[5] However, the introduction of more intensive and flexible insulin regimens (ie, multiple daily insulin injections and insulin pumps) may be a contributing factor in people with diabetes by increasing fat accumulation in spite of improved metabolic control.[6,7]

Insulin resistance and cardiovascular risk factors are associated with increased fat mass.[8,9] Obese (OB) people with T1D have lower insulin sensitivity and a higher cardiovascular risk profile than the non-OB people with T1D.[10–13] Underweight (UW) affects a minority of the pediatric population.[14] However, data in adults suggest that UW individuals with established T1D are more prone to diabetic ketoacidosis and severe hypoglycemia than those with normal weight (NW).[15] Therefore, the increase in the amplitude of the deviation in excess or decrease from the median body mass index (BMI) for age and gender is associated with increased health risk for children and adolescents with T1D. Consequently, it is crucial to identify subjects with at risk BMI and to ensure specific care for managing children with BMI in the UW and overweight (OW)/obesity categories as well as to prevent these conditions.

To the best of our knowledge, there is a scarcity of available data on the prevalence and the geographical distribution of UW, OW, and obesity in large cohorts of children and adolescents with T1D.[16–18]

A previous study based on the DPV (Diabetes-Patienten-Verlaufsdokumentation) data reported that BMI of children and adolescents with T1D is higher compared with healthy children measured in the same year.[19] Especially, very young children and adolescent girls were at risk for OW independent of annual trends. Apart from a study comparing UW, OW, and obesity in children with T1D conducted in Germany, Austria, and United States,[14] there is a lack of international data using the BMI-SD score (BMI-SDS) of the World Health Organization (WHO).[20,21]

Therefore, the aims of this study were to assess the prevalence of UW, OW, and obesity of children and adolescents with T1D in a large international cohort of children and adolescents and to investigate the association between the BMI-SDS and gender, age, duration of diabetes, treatment regimen, and metabolic control.

2 | METHODS

The analysis was based on data from the SWEET "Better control in Pediatric and Adolescent diabete**S**: **W**orking to cr**E**ate C**E**n**T**ers of Reference," a prospective, multicenter, standardized diabetes patient

registry. SWEET is an international consortium of pediatric diabetes centers created with the aim of improving the care of children with T1D through sharing the best practices and the collection of clinical outcome data in large cohorts of patients.[22] Currently, the SWEET network includes 55 pediatric diabetes centers from all continents. For the data collection, centers used the DPV software (https://sweet.zibmt.uni-ulm.de/software.php), DIAMAX Digital Exchanges, data download of existing registries or local databases. Anonymized demographic and clinical data were transferred twice yearly to the SWEET database at the Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany.[23] Inconsistent and implausible data were reported back for verification or correction after each data upload.

As of March 2017, 374 728 visits by 34 542 patients with diabetes were available in the SWEET database. For the present analysis, patients aged 2 to 18 years with T1D and duration of diabetes ≥1 year were included. Patients without documentation of gender, age, duration of diabetes, and BMI-SDS were excluded (Figure 1). Datasets were aggregated over the most recent year of treatment for each patient. In the final study cohort, 23 026 youths with T1D were included. The current analysis involved 25 European countries (42 centers) and 12 countries (13 centers) outside Europe.

Height was measured in 0.5 cm and weight was determined in kilogram. The BMI was calculated as weight (kilograms) divided by height (meters) squared. BMI-SDS was calculated using the WHO BMI charts.[22] Children were categorized as UW (BMI-SDS < −2SD), NW (2SD ≤ BMI-SDS ≤ +1SD), OW (+1SD < BMI-SDS ≤ +2SD), and OB (BMI-SDS > +2SD).[24]

Metabolic control was assessed by glycated hemoglobin (HbA1c), which was measured locally in each center. To adjust for differences between laboratories, multiple of the mean (MOM) method was used to mathematically standardize HbA1c values to the reference range of the Diabetes Control and Complications Trial (DCCT, 21-43 mmol mol^{-1} [4%-6%]).[25] Treatment modality was defined as conventional therapy (CT, ≤3 injection time points per day), intensified conventional therapy (ICT, 4-8 injection time points per day), and insulin pump (continuous subcutaneous insulin infusion [CSII]). Insulin dose was defined as the total daily units of insulin divided by the body weight in kilograms. Age was classified into 2 to <10, 10 to <13, 13 to <16, 16 to ≤18 years. Duration of diabetes was grouped into <2, 2 to <5, and ≥5 years.

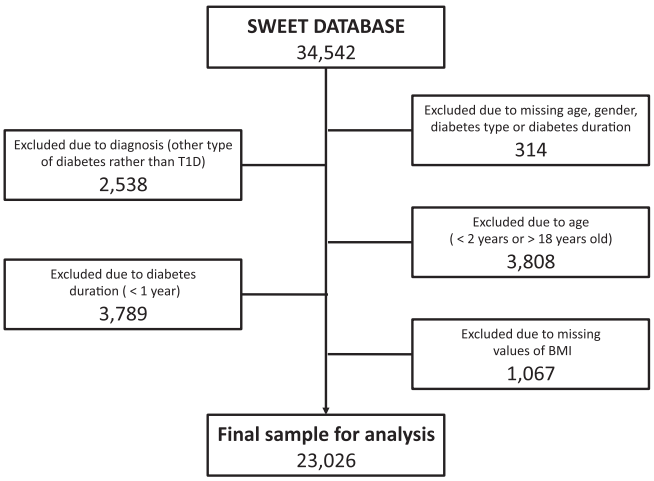

FIGURE 1 Selection of study population

2.1 | Statistical analysis

Results are presented as median with quartiles or numbers and percentages. Wilcoxon, Kruskal-Wallis and χ^2-tests were performed to compare demographic characteristics and clinical outcomes. To adjust for multiple testing, *P*-values were corrected by false discovery rate (FDR).

Hierarchic regression models were adjusted for age, gender, and duration of diabetes. In order to account for variation among pediatric diabetes centers, center was entered as a random effect in the models. Adjusted mean with 95% confidence intervals were used to describe the differences. To adjust for multiple comparisons, Tukey-Kramer test was used.

A two-sided *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using Statistical Analysis Software 9.4 (SAS, SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

Clinical characteristics of study participants are shown in Table 1. In both genders, diabetes duration, BMI, HbA1c, and insulin dose per kg body weight significantly (all $P < 0.0001$) increased with age. Moreover, the proportion of subjects treated with the ICT significantly increased by age category whereas the proportion of those treated with pumps significantly decreased ($P < 0.0001$).

The prevalence of UW, NW, OW, and obesity was: 1.4%, 69.0%, 22.3%, and 7.3% in males and 0.6%, 65.4%, 27.2%, and 6.8% in females. Overall, the prevalence of UW was significantly higher in males than in females ($P < 0.0001$), whereas that of OW was significantly higher in females ($P < 0.0001$). In the youngest age group, the prevalence of obesity was significantly higher in males than females (M: 9.6% vs F: 6.2%; $P < 0.0001$) whereas the opposite was found in the eldest (M: 6.2% vs F: 7.8%; $P < 0.0001$). In children older than 10 years, the prevalence of OW was significantly higher in females (F: 28.2% vs M: 21.5%; $P < 0.05$) whereas the prevalence of UW was significantly higher in males (M: 1.65% vs F: 0.67%; $P < 0.0001$) (Figure 2).

3.1 | Adjusted results

Adjusted for age and gender BMI-SDS significantly increased with diabetes duration (<2 years: 0.38 ± 0.05; 2-5 years: 0.44 ± 0.05; and >5 years: 0.50 ± 0.04; $P < 0.0001$). However, BMI-SDS significantly ($P < 0.0001$) increased by diabetes duration just in females (<2 years: 0.39 ± 0.05; 2-5 years: 0.49 ± 0.04; and >5 years: 0.60 ± 0.04) but not in males (<2 years: 0.39 ± 0.06; 2-5 years: 0.41 ± 0.05; and >5 years: 0.41 ± 0.05; *P* = not significant, NS).

Adjusted for age and duration of diabetes, females had significantly higher BMI-SDS than males (0.54 ± 0.05 vs 0.40 ± 0.05, $P < 0.0001$). Similar to unadjusted data, BMI-SDS in males

TABLE 1 Unadjusted clinical characteristics of the entire study cohort by age category and gender

	2 to <10 years		10 to <13 years		13 to < 6 years		16 to 18 years		Total	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Number	2407	2241	2180	2162	2848	2860	4414	3914	11 849	11 177
Age (y)	7.6 (6.0 8.9)	7.8 (6.1 9.0)	11.7 (10.9 12.3)	11.6 (10.8 12.4)	14.6 (13.8 15.3)	14.6 (13.8 15.3)	17.6 (16.9 17.9)	17.6 (16.9 17.9)	14.5 (10.9 17.2)	14.3 (10.9 17.0)
Diabetes duration (y)	3.4 (2.0 5.2)	3.1 (1.9 4.8)	5.0 (2.8 7.6)	4.6 (2.5 7.3)	5.9 (3.2 9.3)	5.9 (3.5 9.1)	7.1 (4.2 11.1)	7.7 (5.1 11.3)	5.3 (3.0 8.6)	5.5 (3.1 8.7)
Weight (kg)	25.0 (20.8 30.0)	25.0 (20.8 30.0)	39.6 (34.4 45.8)	40.6 (35.0 48.1)	56.5 (48.3 65.5)	56.8 (50.0 64.3)	69.2 (62.4 77.0)	63.5 (56.9 70.9)	54.0 (35.6 68.0)	52.8 (36.2 63.6)**
Height (cm)	124.2 (114.0132.6)	124.7 (114.0132.6)	147.0 (141.0153.0)	148.5 (142.0155.0)	166.8 (158.8173.5)	161.5 (156.8166.5)	176.7 (171.5181.9)	164.5 (160.0169.0)	164 (142.2175.7)	158.0 (142.6165.0)**
BMI (kg m^{-2})	16.5 (15.6 17.7)	16.5 (15.5 17.7)	18.1 (16.7 20.0)	18.4 (16.9 20.4)	20.1 (18.3 22.4)	21.6 (19.5 24.1)	22.1 (20.3 24.3)	23.4 (21.3 25.9)	19.7 (17.4 22.4)	20.7 (17.6 23.7)
BMI-SDS	0.62 (0.01 1.28)	0.53 (−0.04 1.12)	0.53 (−0.15 1.21)	0.42 (−0.22 1.11)	0.42 (−0.29 1.12)	0.67 (0.01 1.30)	0.37 (−0.3 1.03)	0.73 (0.01 1.35)	0.47 (−0.21 1.14)	0.61 (−0.02 1.25)**
HbA1c (%)	7.50 (6.93 8.19)	7.47 (6.86 8.21)	7.70 (7.05 8.52)	7.71 (7.07 8.52)	7.98 (7.17 9.05)	8.08 (7.26 9.19)	7.95 (7.13 9.10)	8.15 (7.31 9.40)	7.80 (7.07-8.75)	7.88 (7.14 8.89)**
Insulin/BW (U × kg^{-1} × day^{-1})	0.69 (0.56 0.82)	0.74 (0.61 0.87)	0.76 (0.62 0.92)	0.84 (0.68 1.01)	0.91 (0.72 1.09)	0.90 (0.71 1.07)	0.87 (0.69 1.05)	0.83 (0.66 1.00)	0.81 (0.64 0.99)	0.82 (0.66 1.00)*
CT (%)	14.3	13.7	11.0	10.8	9.9	10.4	12.3	11.6	11.9	11.6
ICT (%)	30.9	29.8	37.9	38.5	41.3	40.9	45.1	43.6	39.8	39.0
CSII (%)	54.8	56.6	51.1	50.7	48.7	48.6	42.6	44.8	48.3	49.4
Underweight (%)	0.62	0.36	1.15	0.74	1.75	0.77	1.84	0.56	1.40	0.60**
Normal weight (%)	64.7	70.0	66.2	70.1	69.3	62.8	72.5	61.6	69.0	65.4**
Overweight (%)	25.1	23.4	24.1	22.9	22.8	29.5	19.4	30.1	22.3	27.2**
Obese (%)	9.6	6.2	8.6	5.3	6.1	6.9	6.2	7.8	7.3	6.8

Abbreviations: BMI, body mass index; BMI-SDS, body mass index-SD score; BW: body weight; CT, conventional therapy (0-3 injection time points per day); HbA1c, glycated hemoglobin; ICT, intensified conventional therapy (4-8 injection time points per day); CSII, continuous subcutaneous insulin infusion.
Data are shown as median with quartiles or as percentages.
Males vs females (total samples): *$P < 0.01$; **$P < 0.0001$.

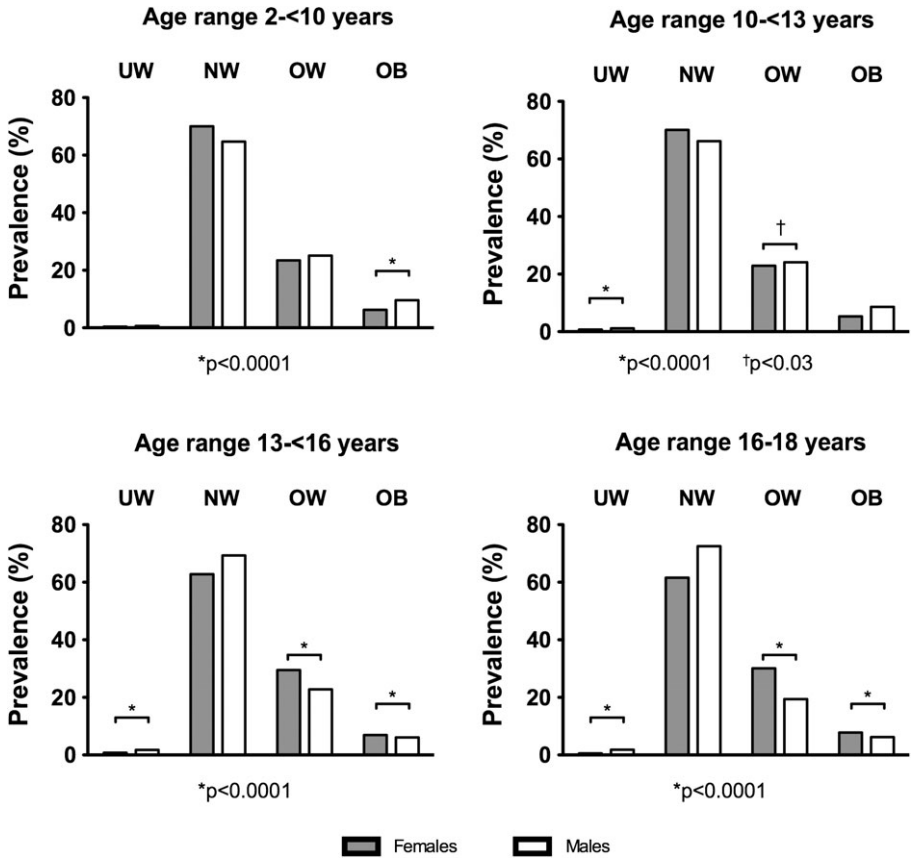

FIGURE 2 Prevalence (%) of underweight (UW), normal weight (NW), overweight (OW), and obesity (OB) by gender and age categories. Children were categorized as UW (BMI-SDS < −2SD), NW (−2SD ≤ BMI-SDS ≤ +1SD), OW (+1SD < BMI-SDS ≤ +2SD), and OB (BMI-SDS > +2SD) in according with World Health Organization (WHO) standards. *P < 0.0001; †P < 0.03

significantly decreased from the first to the third age category (P < 0.0001), whereas BMI-SDS in females showed a significant reduction from the first to the second and the third age category (P < 0.0001), followed by a significant increase in the fourth age category (P < 0.05) (Figure 3).

HbA1c was significantly higher in females (8.20% ± 0.10% vs 8.06% ± 0.10%, P < 0.0001). In both genders, HbA1c was significantly (P < 0.05) higher in UW and OB subjects than in NW persons (Figure 4). In males, HbA1c was significantly (P < 0.05) higher in UW and OB than in OW subjects. In females, HbA1c was significantly (P < 0.001) higher in OW than in normal subjects. No other significant differences were found among BMI categories.

BMI-SDS was not different in children treated with CT (0.42 ± 0.05), ICT (0.48 ± 0.05), or CSII (0.48 ± 0.05) (all P > 0.53). Daily insulin dose per body weight for UW subjects was significantly higher than in the other BMI categories (P < 0.01). Daily insulin dose per body weight was not significantly different between NW, OW, and OB youth and between MDI and insulin pump users. Similar results were found analyzing Norther vs Southern Europe only (data not shown).

4 | DISCUSSION

The mean prevalence of OW and obesity was approximately 30% in the sample of youth participating in this study. This result is in accordance with the reported prevalence in the general population, especially in industrialized countries.[26] Therefore, it is likely that the impact of factors such as genetic predisposition and the pressures from an obesogenic environment in promoting excess body fat accumulation in children and adolescents also impact youth with T1D. This is in spite of exposure to a nutritional education program and to regular clinical follow-up, which should theoretically contribute to maintenance of body weight.[27]

However, the main finding of this large worldwide study of children with T1D was that diabetes duration, adjusted for age, was significantly associated with higher BMI-SDS.[28,29] Type 1 diabetes and its treatment therefore appear to promote excess weight gain. Several factors, which are common in adolescents with or without T1D, such as sedentary behavior, reduced exercise (especially in females), and unhealthy eating habits, may contribute to favor a positive energy balance.[30,31] Other factors favoring body fat accumulation are specific to diabetes, including extra calorie intake to prevent or correct hypoglycemia, the consumption of low carbohydrate high fat foods, to reduce postprandial glucose increase, and the chronic exposure of the peripheral tissues to non-physiologic hyperinsulinemia due to the subcutaneous insulin injections or infusion via insulin pump.[32–42] Nutritional strategies to reduce nocturnal hypoglycemia, if insulin pump or long-acting analog insulin (such as glargine or degludec insulin) are not used, include the ingestion of a bedtime snack containing carbohydrates and protein, although the American Diabetes Association

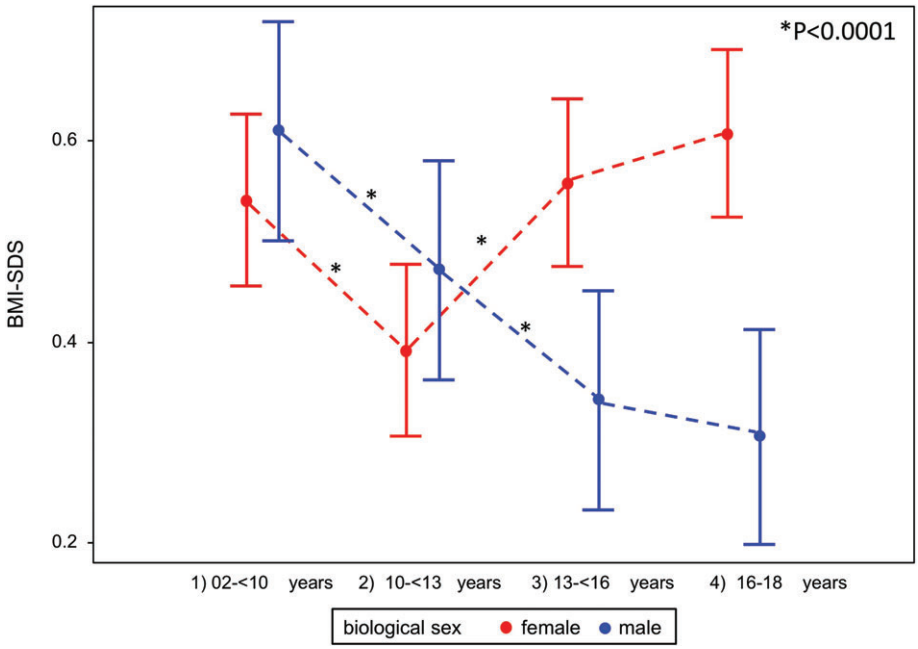

FIGURE 3 Body mass index-SD score (BMI-SDS) compared by age groups and gender adjusted for duration of diabetes. Hierarchic regression model with center as random variable was applied. Data are shown as least-squared means and 95% confidence intervals. Females (red dots): 2 to <10 years vs 10 to <13 years, *P < 0.001; 10 to <13 years vs 13 to <16 years, *P < 0.0001; 13 to <16 years vs 16 to 18 years, P = not significant, NS. Males (blue dots): 2 to <10 years vs 10 to <13 years, *P < 0.001; 10 to <13 years vs 13 to <16 years, *P < 0.0001; 13 to <16 years vs 16 to 18 years, P = not significant, NS

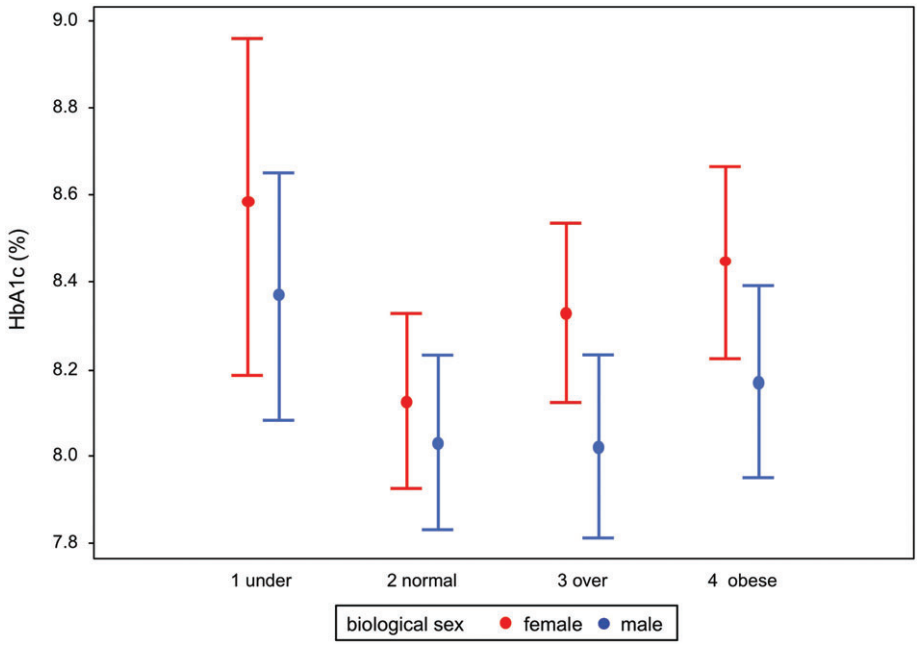

FIGURE 4 HbA1c (%) compared by body mass index-SD score (BMI-SDS) (categorical) and gender adjusted for age (categorical) and diabetes duration (categorical). Hierarchic regression model with center as random variable was applied. Data are showed as least-squared means and 95% confidence interval. Females (red dots): underweight (UW) vs normal weight (NW) P < 0.05; NW vs overweight (OW) P < 0.0001; OW vs obese (OB) P = not significant, NS. Males (blue dots): UW vs NW P < 0.01; NW vs OW P = not significant, NS; OW vs OB P < 0.05

(ADA) and the Endocrine Society reported the absence of consensus on this practice.[32] Moreover, nocturnal hypoglycemia in people without diabetes stimulates spontaneous food intake the following morning, with special preference for carbohydrates.[33] Similar mechanisms may contribute to the frequently observed body weight gain in insulin-treated patients. Due to the strong relationship between carbohydrate intake and postprandial glucose profile, modification of diet composition, with a reduction of carbohydrate, could be a potential strategy for limiting postprandial glucose excursions and fluctuations at least in the short term, although appropriate carbohydrate and fat intake was associated with lower HbA1c.[34,37–39] Moreover, a low carbohydrate intake is associated with less favorable dietary

nutrient composition, leading to overconsumption of protein and fat.[35,36,40] Additionally, subcutaneous insulin injection and infusion exposes the body to higher peripheral insulinemia than that physiologically secreted by the pancreas in non-diabetic subjects[41]; this chronic hyperinsulinemia promotes fat deposition.[42]

Data from the DCCT showed that those subjects exposed to intensive insulin therapy compared to those on CT had a reduced incidence and progression of microvascular complications, reduced risk factors for macrovascular complications, and lower incidence of major cardiovascular disease events.[6,43,44] While these outcomes are favorable, intensive treatment was also associated with a higher incidence of excess weight gain, central obesity, insulin resistance, dyslipidemia, and elevated blood pressure. Accordingly, follow-up of DCCT subjects in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study reported important changes in lipid levels and blood pressure in subjects with excessive weight gain with intensive therapy that were similar to those seen in the insulin resistance syndrome.[45] BMI in children with T1D using intensive insulin regimens is reported increased compared with children treated with less intense therapy (≤3 insulin injections per day).[46,47] On the contrary, the results of our study showed that, adjusting for confounders, BMI-SDS was not affected by the treatment regime. This is in accordance with the data reported by a study with German and Austrian children and adolescents.[48] The most likely explanation of our findings is that lower insulin dose per kg body weight in subjects using insulin pump compared to MDI contributes to reduced insulin exposure and therefore less fat deposition in the peripheral tissues.[41,42,49] Interestingly, in our population the use of pumps decreased with age, in agreement with previous studies.[50,51] Several factors contribute to this finding, such as the decreasing influence of parents in diabetes management during puberty, the impact of the peer group and the comparison within other adolescents, etc.[52] Some of these factors also affect lifestyle, diet, and physical activity, potentially contributing to adiposity accumulation in adolescence.[21]

In both genders, BMI-SDS decreased from prepuberty to puberty, then further decreased in the postpubertal age category for males but increased in females. The difference between genders is likely the result of greater fat gain during and after puberty for girls.[53] Three main factors may contribute to this finding: higher insulin resistance in females than males, alterations in GH/IGF-1 axis in patients with T1D, and the influence of sex steroids.[6] Selective insulin resistance during puberty leads to compensatory hyperinsulinemia, amplifying insulin's effect on amino acid metabolism and thereby facilitating protein anabolism.[54] This physiologic process is increased in adolescents with T1D due to lower insulin sensitivity than non-diabetic peers.[55] Abnormalities of the growth hormone/IGF-1 axis have been reported in adolescents with T1D, with increased GH secretion and incomplete suppression of GH by IGF-1, leading to a higher risk of hypoglycemia and weight gain.[56] Girls seem to be more sensitive to GH/IGF-1 perturbations than boys, due to their much lower increase of testosterone.[57]

This study also found an association between BMI-SDS and the metabolic control. UW and OB children and adolescents had significantly higher HbA1c than NW patients. The cross-sectional design of the study did not allow assessment of the cause-effect relationship between variables. Nevertheless, in accordance with the available evidence, inadequate diabetes control leading to chronic hyperglycaemia is likely associated with energy loss via glucosuria and subsequent weight reduction, spontaneous reduction of food intake promoted by ketoacidosis condition, and increased energy expenditure due to increased protein turnover and gluconeogenesis.[58] The high HbA1c found in subjects with a high BMI-SDS may be due to chronic positive energy balance promoted by inappropriate dietary behavior and eating disorders accompanied by inadequate insulin treatment, which are more common in adolescents than in younger children.[36,59,60]

The strengths of this study were: the large sample size, a worldwide dataset, and the SWEET data quality control. Weaknesses include the fact that the SWEET registry is not population-based and the researchers did not have access to subjects' ethnic backgrounds, nutritional habits, data on adjunctive therapies, different insulin regimens used, or physical activity history. Therefore, prevalence rates are not applicable to the entire population of children and adolescents with T1D. Additionally, BMI-SDS, though widely accepted in large epidemiological studies as a reasonably accurate measure of body size and an index of fatness, is not actually a measure of fatness. Availability of a direct measure of body fat mass might provide a better explanation of the relationship between adiposity and contributing variables. Assessment of body fat distribution could also be useful, as it may be a stronger factor than total fat mass in promoting cardiovascular risk.[61] Although this study assessed BMI by the WHO charts, comparisons between study subjects and appropriate age and gender populations or other cohorts of diabetic children and adolescents would be useful for future analysis.

In conclusion, 1 of 3 children and adolescents with T1D was OW or OB whereas 1 of 100 was UW. On average, females had higher BMI-SDS than males and BMI-SDS increased with diabetes duration. UW and OB children and adolescents had the higher HbA1c. These results emphasize the need for developing further strategies to prevent and treat excess fat accumulation in T1D as it is strongly recommended for the general population.

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Conflict of interest

We declare that we have no conflict of interest.

Author contributions

C.M. wrote the manuscript. N.H.B., M.K., A.S., A.V., K.C., S.J., C.L., A.P.-L., P.T.-H., C.D.B., Z.S., V.C., J.S., D.P., C.K.G., S.S., N.B., R.H., G.T.A., L.P., A.L.P., M.M. researched data and critically reviewed/edited the manuscript. A.S. analyzed the data. All co-authors approved the final version to be published.

ORCID

Niels H. Birkebaek http://orcid.org/0000-0001-6268-6464
Jannet Svensson http://orcid.org/0000-0002-9365-0728
Daniele Pacaud http://orcid.org/0000-0001-6337-7241
Shlomit Shalitin http://orcid.org/0000-0002-2729-9175
Natasa Bratina http://orcid.org/0000-0001-8185-5366
Ragnar Hanas http://orcid.org/0000-0001-8372-030X
Marco Marigliano http://orcid.org/0000-0002-3232-8807

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